December 11, 2008

FINDINGS AND RECOMMENDATIONS of the BDCM EXPERT PANEL MEETING SEPTEMBER 22nd and 23rd, 2008

Context:

Health Canada leads the development of the Guidelines for Canadian Drinking Water Quality to establish maximum acceptable concentrations (MAC) of contaminants in drinking water, based on up-to-date scientific and technical information. The Guideline Technical Document for trihalomethanes (THMs) in drinking water, which includes a specific guideline for Bromodichloromethane (BDCM), was published in May 2006. The document establishes a MAC of 0.1 mg/L (100 µg/L) for THMs, as a running annual average of quarterly samples. This MAC is based on the health effects of chloroform, and applies to the total concentration of chloroform, BDCM, dibromochloromethane (DBCM) and bromoform.

The Guideline Technical Document also establishes a MAC of 0.016 mg/L (16 µg/L) for BDCM in drinking water. This MAC is based on a cancer endpoint and is designated as a "not-to-exceed" value as a precaution for potential adverse reproductive effects. Health Canada had used the 1987 NTP study, which used corn oil as a vehicle, as the key study to derive a MAC based on BDCM's carcinogenic potential.

Since the development of the MACs, several new relevant scientific papers have been published on the health effects of BDCM and of THMs. The 2006 NTP study on BDCM used drinking water as the vehicle, and it suggests that BDCM in drinking water may not cause cancer in laboratory animals, which contradicts the findings from the 1987 NTP study. New epidemiological studies have been published on the reproductive effects of BDCM, which are not showing an association between exposure to BDCM and adverse reproductive results.

Consequently, Health Canada has identified a need to review the scientific evidence now available to ensure the approach used to derive the BDCM guideline is still appropriate and to determine whether a MAC specific to BDCM is still necessary and if so, at what level.

As part of this review, Health Canada commissioned three reports (two consultant reports and one internal report) to assess current science. The first report, entitled "*Evaluation of the vehicle effects on the internal dose and carcinogenicity of BDCM based on PBPK modeling and mode-of-action*" (Krishnan, 2008a), examined the NTP 1987 and 2006 data, in addition to the current literature on the potential carcinogenic effects of BDCM exposure. The second report entitled *"Potency estimation for BDCM based on PBPK models"* (Walker, 2008) focussed on the statistical manipulation of the data and modeling to calculate tumorogenic doses (TDs), the increases in tumor rates over background. The final report, *"Cancer dose-response analysis for BDCM"* (Krishnan, 2008b), converted the TDs from Walker's report into human environmental doses using a PBPK model.

These reports were used as a starting point for discussions with experts, which marks the beginning of the review process of this guideline. A panel of experts was convened in September 2008 to provide expert advice and to make recommendations to Health Canada and to the Federal-Provincial-Territorial Committee on Drinking Water (CDW) regarding BDCM in drinking water. Advice was sought from the Expert Panel on three specific issues of concern:

1- Reproductive and developmental toxicity of BDCM;
2- Carcinogenicity of BDCM;
3- Risk assessment approach to develop BDCM guideline.

The Expert Panel reached a consensus on all key issues identified, and its main conclusions and recommendations to Health Canada and the Federal-Provincial-Territorial Committee on Drinking Water on each issue are provided below.

Expert Panel Members:

Linda Dodds, Dalhousie University, Canada
Kannan Krishnan, Université de Montréal, Canada
Rex Pegram, U.S. Environmental Protection Agency, USA
Robert Tardiff, The Sapphire Group, Inc., USA
Richard Bull, Pacific Northwest National Laboratory, USA
John Fawell, Independent Consultant on Drinking Water and Environment, UK

Issue 1: Reproductive and developmental effects

Epidemiological evidence

At the time of the update of Health Canada's Guideline Technical Document on THMs, there was some epidemiological evidence for an association of BDCM exposure with reproductive and developmental effects (i.e., spontaneous abortion). The MAC of 16 µg/L for BDCM in drinking water was based on a cancer endpoint, but identified as a "not-to-exceed" value as a precautionary approach for potential reproductive effects.

Recent evidence, from epidemiological studies with improved protocols and exposure assessment technologies, demonstrates no or inconsistent association for most reproductive or developmental endpoints with BDCM exposure at current levels.

Based on their knowledge of the science at the time of the meeting, the expert panel on BDCM agreed to the following consensus responses to Health Canada's questions:

Question from Health Canada: Does the current weight of evidence from epidemiological studies support an association between adverse reproductive and developmental effects in human and environmental exposure to BDCM?

Response from the Expert Panel: *"Overall, the evidence from epidemiological studies is inconsistent and by international standards, the current weight of evidence is not sufficient to support an association between adverse reproductive and developmental effects in humans and environmental exposures to BDCM.*

Question from Health Canada: Do you know of any new or upcoming studies that could have an impact on the weight of evidence for an association of adverse reproductive and developmental effects in human with environmental exposure to BDCM?

Response from the Expert Panel: L. Dodds identified four groups of studies currently underway whose findings will need to be considered in the future, once they are completed and published:

- Levallois et al.
- U.S. EPA, National Center for Environmental Assessment, Dr. Michael Wright
- Nieuwenhuijsen et al.
- Dodds et al.

Toxicological evidence

As cancer was considered to be the endpoint of concern to derive the 2006 MAC for BDCM, the toxicological effects of BDCM on reproduction and development in animals were not considered in the derivation of the guideline value. In animal models, the adverse reproductive and developmental effects of BDCM were observed only at very high doses and were inconsistent among animal models. Results also varied according to the method of BDCM administration and only limited data explore modes of action for reproductive and developmental toxicity.

Based on their knowledge of the science at the time of the meeting, the expert panel on BDCM agreed to the following consensus responses to Health Canada's questions:

Question from Health Canada: Does the current weight of evidence from toxicological studies support an association between adverse reproductive/developmental effects and BDCM exposure in animals?

Response from the Expert Panel: *"Although BDCM has been shown to cause adverse reproductive effects in animals, these have only been observed at maternally-toxic doses which are 5000 to 15000 times higher than levels found in drinking water. Overall, the current weight of evidence from toxicological studies does not support an association between adverse reproductive/developmental effects and exposure to BDCM at concentrations that occur in chlorinated drinking water.* "

Question from Health Canada: Do you know of any new or upcoming studies that could have an impact on the weight of evidence for an association of adverse reproductive and developmental effects in animals with exposure to BDCM?

Response from the Expert Panel: R. Pegram identified several new studies, that are underway but not yet published, and whose findings will need to be considered in the future:

- Lasley et al., (University of California, Davis). 1. Further analysis of the effect of BDCM on human placental cell differentiation in vitro. 2. Effects of DBP mixtures on human placental cell function in vitro.
- Bielmeier et al., (U.S. EPA). BDCM-induced reduction in LH secretion in the SD rat.
- Narotsky et al. (U.S. EPA). Effects of inhaled BDCM on pregnancy and relevant endocrine functions.

Issue 2: Carcinogenicity

The current guideline for BDCM in drinking water was developed using the 1987 NTP study as the key study, which used corn oil as a vehicle, and found increased tumours in F344/N rats. The 2006 NTP study found no evidence of increased carcinogenic activity of BDCM in male F344/N rats or female B6C3F1 mice when BDCM was administered via drinking water.

Based on their knowledge of the science at the time of the meeting, the expert panel on BDCM agreed to the following consensus responses to Health Canada's questions:

Question from Health Canada: Considering the findings from the new NTP (2006) study and from other recent toxicological data, does the current weight of evidence support BDCM carcinogenicity in animals?

Response from the Expert Panel: "*The evidence from a lifetime study of BDCM given to rodents by corn oil gavage is that it is an animal carcinogen. However, a second NTP lifetime study,*

which tested lower doses of BDCM in drinking water does not support this determination. The combined data from the two studies do not support a linear dose response."

"Some shorter term studies demonstrate the development of aberrant crypt foci in the rat large intestine when BDCM is given in drinking water, which suggests that BDCM may play a role in carcinogenesis."

Question from Health Canada: At the time of the expert panel meeting, BDCM was classified in Group II − probably carcinogenic to humans, with sufficient evidence in animals and inadequate evidence in humans (Health Canada, 1994). Should BDCM still be considered probably carcinogenic to humans?

Response from the Expert Panel: *The NTP 2006 drinking water study diminishes the weight of the evidence that BDCM is "probably" carcinogenic in humans. However, the possibility that a mutagenic mode of action contributes to the carcinogenic effects of BDCM in the intestine cannot be dismissed. Therefore, the Panel concluded that the NTP (2006) data alone are not sufficient to change the classification to "possibly" carcinogenic in humans.*

Issue 3: Risk assessment

BDCM is classified in Group II, "*probably carcinogenic to humans"*, based on sufficient evidence in animals, but insufficient evidence from human epidemiological studies. Because BDCM is considered to be "probably" carcinogenic to humans, the MAC is derived based on the estimated lifetime cancer risk. Health Canada considers a lifetime cancer risk range of 10^{-5} to 10^{-6} to be "essentially negligible". The 2006 guideline was derived using the Linear Multistage [LMS] method of Howe (1995), based on the results from the 1987 NTP key study. The MAC for BDCM in drinking water is considered as a "not-to-exceed" value, rather than an annual average, as a precautionary approach for potential reproductive effects.

Based on their knowledge of the science at the time of the meeting, and on the previous discussions on Issue Sheets 1 and 2, the expert panel on BDCM agreed to the following consensus responses to Health Canada's questions:

Question from Health Canada: Is the current science sufficient to justify re-assessment of the BDCM guideline?

Response from the Expert Panel: "*Sufficient new evidence exists to support the reassessment of the BDCM guideline."*

Question from Health Canada: Given the total THMs MAC, is the individual MAC for BDCM in drinking water still necessary?

Response from the Expert Panel: *"At this time, it is unlikely to be necessary to retain a BDCM guideline, however, the risk assessment needs to be completed."*

Question from Health Canada: Is the overall proposed approach for risk assessment of BDCM based on carcinogenicity appropriate? If not, what do you recommend? Are there any factors/considerations we omitted?

Response from the Expert Panel: "*Carcinogenicity is the key endpoint for risk assessment. The appropriate dose metric is internal dose, and issues related to human metabolism and kinetics need to be considered in the assessment. Two low dose extrapolation approaches should be considered for illustrative purposes (linear vs non-linear). An approach based on carcinogenicity is most likely to be protective of non-cancer health effects including reproductive/developmental effects.*"

Question from Health Canada: Should reproductive and developmental effect be considered as key endpoints when deriving the MAC for BDCM? If yes, which animal model would be appropriate, which key study should be used for reproductive/developmental effects in animals, and what would be the NOAEL?

Response from the Expert Panel: *"Reproductive and developmental effects must be considered in the risk assessment, although they are unlikely to be the key endpoint. Two drinking water studies could be used (Christian et al., 2001 & 2002); each study generated a NOAEL."*

Question from Health Canada: Should "not-to-exceed" still be applied to the BDCM guideline value to protect the Canadian population against potential adverse reproductive and developmental effects of BDCM in drinking water?

Response from the Expert Panel: *"Since the current weight of evidence does not support the need for a BDCM guideline based on reproductive/developmental toxicity, the concept of "not-to-exceed" for BDCM is no longer applicable."*

Additional Comments from Expert Panel

Based on their knowledge of the science at the time of the meeting, and on the discussions held during the meeting, the expert panel on BDCM suggested that Health Canada also take into consideration the following comments when updating its Guideline Technical Document:

- *"Water suppliers should keep disinfection by-products as low as possible at all times without compromising disinfection."*
- *"New human data on the absorption of THMs via inhalation and skin contact may need to be considered to further inform the risk characterization."*
- *It was noted that an association between exposure to total THMs and adverse reproductive outcomes may exist.*
- *"It remains important that Health Canada continue to monitor the emerging scientific evidence in order to ensure that the guidelines for DBPs are kept up to date within a reasonable timeframe."*